REMARKS

Claims 9, 10, and 15-25 are pending in this patent application.

Claims 9 and 10 stand rejected under 35 U.S.C. § 103 as being unpatentable over Cotten, *et al*.. Applicants respectfully request reconsideration of this rejection, as the Cotten reference clearly fails to suggest numerous aspects of the claimed inventions. Claim 9, for example, recites numerous 2'-O-substituents that are neither disclosed nor suggested by the Cotten reference. Claim 10 is directed to 2,6-diamino-9-(*β-D*-ribofuranosyl)purines, which similarly are not disclosed or suggested by the Cotten reference. These facts -- in and of themselves -- mandate withdrawal of the obviousness rejections. Indeed, obviousness is established only when the prior art suggests the claimed invention. *In re Shaffer*, 108 U.S.P.Q. 326 (C.C.P.A. 1956) (references, viewed by themselves and not in retrospect, must suggest doing what applicant has done). Since the Cotten reference clearly does not suggest the claimed compounds, reconsideration and withdrawal of the rejection of claims 9 and 10 respectfully is requested.

Claims 15 and 16 stand rejected under 35 U.S.C. § 103 as being unpatentable over Cotten, *et al*. and Iribarren, *et al*. in view of Wagner, *et al*, which has been asserted to disclose "2'-O-ethyl guanosine." (Office Action mailed November 10, 1994, at page 7). Applicants traverse this rejection by demonstrating

that they were in possession of the relevant disclosure of the Wagner reference by at least January 11, 1991, nearly seven months before July 1, 1991, the date on which the reference appears to have even been submitted for publication. Evidence of this is provided by international patent application PCT/US91/00243, which was filed January 11, 1991, designating the United States. A copy of the PCT/US91/00243, published as WO 91/10671, accompanied the Request For Reconsideration mailed March 10, 1995. WO 91/10671 at pages 19-20, for example, discloses oligonucleotides consisting of guanine nucleic acid bases and at least one 2'-O-alkyl group having 1 to 12 carbon atoms. Thus, Applicants antedate the Wagner, *et al.* reference by showing prior invention of all the relevant disclosure of that reference (*i.e.*, 2'-O-ethyl guanosine) according to *In re Stryker*, 168 U.S.P.Q. 372 (C.C.P.A. 1971).

The outstanding Office Action suggests that the removal of the § 103 rejection of claims 15 and 16 is not warranted because Applicants did not cite the page and lines in WO 91/10671 which set forth the subject matter of the claims. (*See*, Office Action at page 2). The patent laws, however, do not require that an applicant seeking to antedate a reference show that they were in possession of their entire invention prior to the effective date of the reference. Rather, all that is required is that an applicant show that they were in possession of the subject matter that has been asserted to render their invention obvious. *In re*

Stryker, 168 U.S.P.Q. 372 (C.C.P.A. 1971). *See also, In re Wakefield*, 164 U.S.P.Q. 636, 639 (C.C.P.A. 1970). Accordingly, Applicants respectfully request withdrawal of the rejection of claims 15 and 16 under 35 U.S.C. § 103.

Claims 15 and 16 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide adequate written description of the phrases "C_4-C_{20} alkyl" and "C_5-C_{20} alkyl". Applicants respectfully traverse this rejection. Page 3 of the specification clearly states that "[i]n some cases it is desirable to provide 2'-O-alkyl groups having long chain alkyl groups (i.e. four or more carbon atoms)." Page 12 of the specification states that "[i]n more preferred embodiments of the present invention R_1 is C_4-C_{20} alkyl and in still more preferred embodiments of the present invention R_1 is C_5 to C_{20} alkyl." Thus, the specification provides adequate written description of the phrases "C_4-C_{20} alkyl" and "C_5-C_{20} alkyl". Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Claims 9-10 and 15-16 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged failure to provide an enabling disclosure. Applicants respectfully request reconsideration of this rejection, as there is no reason of record to believe that persons skilled in the art would not be able to make and use the claimed compounds.

The first paragraph of § 112 requires that the disclosure of a patent application be such that persons skilled in the art, having read the patent application, would be able to practice the inventions described by the claims. That is, the disclosure should be one that enables persons skilled in the art to make and use the claimed inventions. There is no legal requirement that this be done in any particular manner; an enabling disclosure can be provided by the use of illustrative examples or simply by broad terminology. *In re Marzocchi*, 169 U.S.P.Q. 367 (C.C.P.A. 1971). Moreover, a patent application must be deemed to be enabling unless there is reason to doubt the truth of statements contained in the patent application relating to making and using the invention:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must*** be taken as in compliance with the enabling requirements of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.

In re Marzocchi, 169 U.S.P.Q. at 369-370 (emphasis added).

The outstanding Office Action asserts that the specification fails to provide an enabling disclosure as required by § 112. (Office Action at pages 3-4). Significantly, however, the Office Action does not dispute that persons skilled in the art having read the specification would be able to make and use the claimed inventions. Rather, the Office Action suggests that the specification does not comply with § 112 because persons skilled in the art allegedly would have to engage in "undue experimentation" to practice the invention. The Office Action, however, fails to provide any evidence or reasoning indicating that the level of experimentation required to make and use the claimed compounds would be undue within the meaning of the patent laws. Accordingly, the rejection for alleged lack of enablement is improper. *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); *In re Armbruster*, 185 U.S.P.Q. 152 (C.C.P.A. 1975) (Patent Office has the burden of proving that the disclosure does not provide information that is sufficient for one skilled in the art to practice a claimed invention).

The Office Action does provide an analysis of factors to be considered in determining whether the experimentation that would be involved in practicing the claimed inventions would be undue. Significantly, however, this analysis fails to indicate that undue experimentation would be involved in making and using the claimed inventions.

For example, under the heading "Quantity of Experimentation," the Office Action asserts that the alleged absence of "specific disclosures" of procedures in which the claimed compounds can be used would make it difficult for persons skilled in the art to determine "the specific identity" of such compounds. (Office Action at page 4). Nothing could be further from the truth. Indeed, ***no*** experimentation is necessary to determine the identity of the claimed compounds. The claimed compounds are those described by the clear language of the claims. Evaluating the claim language would not involve experimentation, but simply reading the claims. Moreover, the present specification *does* provide "specific disclosures" of procedures in which the claimed compounds can be used to, for example, hybridize complementary RNA or DNA strands. (*See, e.g.*, pages 43-44). Thus, the "Quantity of Experimentation" factor does not indicate the level of experimentation associated with the claimed invention to be undue.

Under the heading "Guidance Provided," the Office Action asserts that "[t]here is little guidance given in the specification as to specific diagnostic, research and therapeutic methods the compounds of the instant invention are to be used in." (Office Action at page 4). However, as noted above, the specification provides detailed procedures demonstrating exemplary use of the claimed compounds, such as for research purposes in hybridizing with complementary RNA or DNA strands.

(*See*, Specification at pages 43-44). These procedures provide considerable guidance as to uses for the claimed compounds. Since there is no requirement that an applicant enable each and every possible use, these detailed procedures provide more than ample guidance.

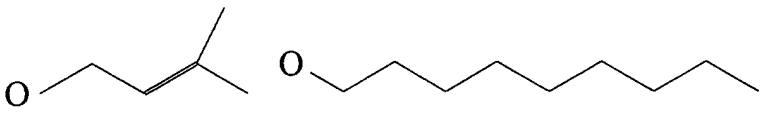
Also under the heading "Guidance Provided," the Office Action asserts that "[t]here is little guidance provided as to the results of the multitude of instantly claimed modifications." (Office Action at page 4). The provision of such results, however, would not help persons skilled in the art practice the inventions. The mere disclosure of a result fails to convey information that would help achieve that result. For example, simply stating that "the puzzle was solved" conveys nothing about how the puzzle was solved. Similarly, simply stating that "compound X has activity Y" does not tell someone how to use compound X. There is no requirement under § 112 that an applicant provides actual and expected results where, as here, persons skilled in the art would otherwise be able to practice a claimed invention.

Under the heading "Working Examples in Disclosure," the Office Action finds fault with the specification because it allegedly does not provide an adequate number of experimental examples providing melting temperatures. (Office Action at page 5). Since it is undisputed that persons skilled in the art would be able to use the claimed compounds, what the Office Action

appears to seek is a recitation of the experimental results observed following such use. However, as noted above, provision of such results would not help persons skilled in the art practice the claimed inventions. The Office Action also asserts that the specification is "woefully inadequate to properly support the thousands of different 2'-O-modifications encompassed by the claims without substantial working examples..." showing results. (Office Action at pages 5-6). Significantly, however, the Office Action fails to indicate any reason to believe that the provided examples are insufficient or that additional examples would be required for persons skilled in the art to avoid "undue experimentation." Given that the disclosure teaches the preparation of numerous examples, there is no reason to believe that one skilled in the art would not be able to make and use the claimed compounds.

Also under the heading "Working Examples in Disclosure," the Office Action asserts that Iribarren, *et al.* teaches that branched 5-carbon modifications at the 2'-O position resulted in severe reduction in hybridization and concludes that a "person skilled in the art would question whether many if not most of the claimed 2'-O-modifications would create a uniformly modified oligonucleotide which could specific [sic] bind to the complementary sequence of DNA or RNA." (Office Action at page 5). Significantly, however, the Iribarren, *et al.* reference does not teach that compounds having bulky 2'-O-substituents do not

hybridize, but, rather, that a compound having a specific 2'-O moiety, 3,3-dimethylallyl, hybridizes less well than other compounds. Indeed, the published literature clearly indicates that the claimed compounds do, in fact, form sufficiently strong hybrids. For example, Guinosso, *et al.*, *Nucleosides & Nucleotides* **1991**, *10(1-3)*, 259, disclose that compounds bearing rather bulky 2'-O-substituents such as 2'-O-nonyl groups form stable hybrids with complementary oligonucleotides (*see, e.g.*, Table 1 on page 260). For the Examiner's convenience, the structures of the O-3,3-dimethylallyl group described in the Iribarren, *et al.* reference and the O-nonyl group of Applicants' claimed invention are compared below.



-O-3,3-dimethylallyl -O-nonyl

As can be seen, the nonyl group is arguably no less bulky than the 3,3-dimethylallyl group. Indeed, the 3,3-dimethylallyl group is merely a straight chain allyl group having a single methyl substitution. Thus, since the Iribarren, *et al.* reference does not teach that a compound having a 2'-O-3,3-dimethylallyl moiety will not hybridize, and since the Guinosso, *et al.* reference teaches that other bulky 2'-O moieties, such as, for example, the 2'-O-nonyl moiety, effectively hybridize to a complementary nucleotide sequence, one skilled in the art would not question

whether the claimed modifications would result in compounds capable of binding to complementary RNA or DNA. Since there is no reason to believe that the claimed compounds will not hybridize to some measurable extent, there is no reason to believe that undue experimentation is required to practice Applicants' claimed invention. Thus, the "Working Examples in Disclosure" factor does not support rejection.

Under the heading "Nature Of The Invention," the Office Action refers to the field of nucleic acids and asserts that there is "an atmosphere for the necessity of extensive research in this burgeoning art area" due to a number of perceived problems. (Office Action at page 6). Even if this assertion were true as it relates to nucleic acids in general and their many possible uses (and Applicants maintain that it is not true), it falls short of establishing that undue experimentation would be necessary to put the claimed compounds to the single use required under § 112. As a preliminary matter, it is not clear how the existence of an "atmosphere for the necessity of extensive research" indicates -- much less demonstrates -- that someone wanting to practice the invention would actually have to engage in undue experimentation. Moreover, the Office Action fails to indicate why the perceived problems listed in the Office Action would be expected to be encountered in making and using the claimed compounds. Indeed, it is clear that there are uses for the claimed compounds in which a number of these perceived

problems would not be encountered. For example, the ability to traverse membranes would not be a concern when using the claimed compounds as research reagents to study hybridization in acellular systems. Thus, the "Nature Of The Invention" does not indicate that undue experimentation would be necessary.

The Office Action at pages 6-7 also evaluates the "State Of The Prior Art." The state of the prior art, however, indicates that any experimentation that would be involved in making and using the claimed compounds is routine in nature and not "undue." As noted in the Office Action, the use of modified nucleic acids is "well documented." The possibility that these same, routine factors might be encountered in using the claimed compounds can hardly be said to render the experimentation associated with such research undue.

Under the heading "Predictability in the Art", the Office Action at pages 7-8 asserts that use of the claimed compounds is unpredictable because the specification fails to provide "the identity of the specific diagnostic, research or therapeutic methods in which applicants intend to employ" such compounds. However, the specification clearly *does* provide the identity of procedures in which the claimed compounds are to be used. For example, as noted above, the specification provides detailed procedures for using the claimed compounds in hybridizing with complementary RNA or DNA strands. Since there is no requirement that an applicant enable each and every

possible use, any failure to identify other uses cannot serve as the basis for finding use of the claimed compounds unpredictable.

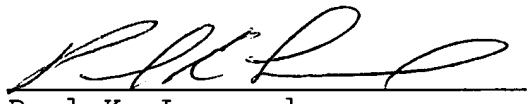
Under the heading "Breadth of Claims" the Office Action at page 8 appears to suggest that undue experimentation would be required because some of the claimed compounds "may be preferred" over others. However, it is not seen how the possibility that some compounds may work better than others would affect the extent to which persons skilled in the art can make and use the compounds. Also, the fact that the claims may be broad fails to support a finding that undue experimentation would be necessary. Even voluminous research is not undue so long as it is of a routine nature. *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Pat. Off. Bd. App. 1986). As noted above, the prior art indicates that the research that would be necessary to make and use the claimed compounds would be of a type routinely encountered. Nothing in the Office Action indicates that the breadth of the claims, by itself, would present an unacceptable impediment to making and using the invention.

Under the heading "Relative Skill in the Art," the Office Action admits that the level of skill in the art is relatively high. Applicants submit that the highly qualified scientific professionals who practice in the art would encounter no difficulty in performing the routine experimentation that would attend practice of the claimed inventions.

In view of the foregoing, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Applicants submit that there is no reason of record to believe that persons skilled in the art of nucleic acid chemistry would not be able to make and use the claimed compounds. Likewise, there is no reason to believe that making and using the claimed compounds would entail experimentation that is undue within the meaning of the patent laws. The claims patentably define the invention over the applied art and are otherwise in] condition for ready allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Respectfully submitted,



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